Kidney International, Vol. 62, Supplement 81 (2002), pp. S34–S45

Biocompatibility of icodextrin

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Peritoneal dialysis (PD) has been a successful form of chronic renal replacement therapy for more than twenty years. In spite of the successes of this therapy, there is a growing awareness that the high glucose content of PD solutions may ultimately compromise membrane performance over time, a realization that underlies the search for, and production of, glucose-free solutions. Icodextrin, one of the second-generation PD solutions, was developed as an alternative to glucose-based solutions to provide a sustained level of ultrafiltration through the use of a glucose polymer as the osmotic agent, and is currently used by more than 9000 patients worldwide. While icodextrin has now proven itself to be clinically useful in the fluid management of PD patients, there are indications that it also may demonstrate improved biocompatibility when compared to the traditional solutions. This review evaluates the biocompatibility of icodextrin versus glucose-based solutions, and shows how this new solution may significantly contribute to an overall therapeutic strategy for improving PD.

BIOCOMPATIBILITY

The peritoneal membrane is a complex tissue that plays a pivotal role in peritoneal cavity homeostasis [1]. The cellular components of the membrane are active in host defense [2–5], maintain a balance of peritoneal coagulant and fibrinolytic activity [6–9], contribute to membrane repair and remodeling of the extracellular matrix [10, 11], and regulate cytokine and chemokine production (Table 1) (abstract; Jörres et al, *Nephrol Dial Transplant* 8:1023, 1993) [12–15]. The membrane itself functions as a semipermeable barrier regulating the selective transport of water and solutes between the systemic circulation and the peritoneal cavity during PD. It is becoming increasingly apparent that, in spite of the success of PD as a renal replacement therapy, chronic exposure to glucose-based solutions may compromise the biological function of the peritoneal membrane [28, 29].

Key words: renal replacement therapy, CAPD, APD, dialysate, membrane permeability, ultrafiltration, peritoneal cavity homeostasis.

As a result of the growing awareness of the potential effects of glucose-based solutions on membrane physiology, there has been an increased emphasis on the development of second-generation PD solutions that reduce or eliminate glucose exposure and are more biocompatible with membrane biological and metabolic processes [30–34].

The biocompatibility of a PD solution can be defined as the ability of a solution formulation to permit long-term dialysis without any clinically significant changes in the functional characteristics of the peritoneum and, as such, is of paramount importance not only in maintaining the health of the membrane, but also in permitting PD to be a successful long-term therapy. The potential role of PD solution biocompatible factors in clinical outcomes is illustrated in Figure 1. Solution components can affect leukocyte, mesothelial cell, endothelial cell, and fibroblast function, resulting in alterations in cytokine, chemokine, and growth factor networks, up-regulation of pro-inflammatory and profibrotic pathways, impaired peritoneal host defense, and the induction of carbonyl and oxidative stress. Such perturbations of normal physiology have been proposed as causative factors contributing to changes in peritoneal structure, such as peritoneal fibrosis, sclerosis and vasculopathy, and changes in peritoneal function, including increased solute permeability and ultrafiltration (UF) failure.

The characteristics of conventional glucose-based dialysis solutions that have been reported to affect the biocompatibility of the formulation include the pH/buffer system, the osmolarity, the glucose concentration, and the glucose degradation product (GDP) profile of that solution. Icodextrin is virtually identical to glucose-based PD solutions in its formulation except for the replacement of glucose with icodextrin as the osmotic agent (Table 2). Icodextrin is a high molecular weight glucose polymer fraction of hydrolyzed corn starch. Briefly, it is a mixture of D-glucopyranose polymers of different chain lengths, between 4 and 250 units, linked by α-(1-4) and α-(1-6) glucosidic bonds, exhibiting a mean molecular weight of 16,200 Daltons (D). The chemical properties of icodextrin produce a colloidal, rather than crystalline osmotic pressure that, in effect, maintains sustained ul-

Table 1. Molecules produced by peritoneal mesothelial cells

Activity	Molecule	Category	References
Host defense	IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-15	Pro- & anti-inflammatory cytokines	[12–16]
	MCP-1, RANTES	Chemokines	[12, 16]
	ICAM-1, VCAM-1	Adhesion molecules	[17]
	PGE_2, PGI_2	Prostaglandins	[18]
	Catalase, SOD, glutathione peroxidase	Anti-oxidant enzymes	[19]
Coagulant and fibrinolytic activity	tPA, uPA, PAI-1, PAI-2	Fibrinolytic enzymes, pro-coagulant enzymes	[6–9]
Membrane repair and remodeling	TGF-β, fibronectin, laminin, collagens type I, III, IV	Growth factors, extracellular matrix components	[20–23]
	MMP-2, MMP-3, MMP-9	Matrix metalloproteinases	[10]
	TIMP-I, TIMP-II, TIMP-III	Tissue inhibitors of MMPs	[10]
	Hyaluronin, HA synthase, decorin, biglycan	Proteoglycans	[24, 25]
Water, glucose transport	AQPs	Aquaporins	[26]
	GLUT	Glucose transporters	[27]

Abbreviations are: IL, interleukin; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T cell expressed and secreted; ICAM, intercellular adhesion molecule; VCAM, vascular cellular adhesion molecule; PGE_2 and PGI_2, prostaglandin E_2 and I_2; SOD, superoxide dismutase; tPA and uPA, tissue-type and urokinase-type plasminogen activator; TGF-β, transforming growth factor-β; MMP, matrix metalloproteinase; TMP, tissue inhibitor of metalloproteinase; HA, hyaluronin; AQP, aquaporin; GLUT, glucose transporters.

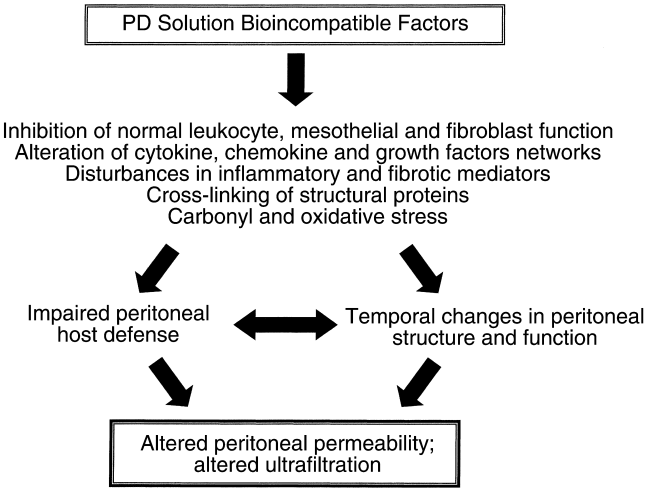

Fig. 1. Potential role of biocompatibility in clinical outcomes. Chronic exposure to bioincompatible PD solutions can result in perturbations in normal cellular physiology. These changes in membrane structure and function can ultimately result in declining peritoneal transport and ultrafiltration, and worsening clinical outcomes.

Table 2. Composition of glucose-based and icodextrin-based PD solutions

Components	Glucose solution	Icodextrin solution
Glucose *g/L*	13.6, 22.5 or 38.6	—
Glucose polymer *g/L*	—	75
Sodium *mEq/L*	132	132
Chloride *mEq/L*	96	96
Calcium *mEq/L*	3.5	3.5
Magnesium *mEq/L*	0.5	0.5
Lactate *mEq/L*	40	40
Osmolality *mOsm/kg*	358, 401, or 511	282
pH	5.2	5.2

trafiltration for the long dwell in both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) [35, 36]. A complete description of the chemical characteristics of icodextrin can be found in Alsop [37], and elsewhere in this Supplement issue of *Kidney International*.

This review discusses the biocompatibility profile of icodextrin PD solution in terms of its potential to avoid glucose and hyperosmolarity-mediated cytotoxicity, and GDP- and advanced glycation end product (AGE)-mediated cellular alterations. Secondly, the contribution of the PD solution *per se* to peritoneal carbonyl stress versus the contribution of the uremic milieu will be described, and the potential benefit of icodextrin in this context reviewed. The role of pH and buffer system will not be a focus of this review because the icodextrin-based solution formulation in this respect is similar to conventional glucose-based solutions.

GLUCOTOXICITY

For the past twenty years, glucose has been used successfully as the osmotic agent in PD solutions. Yet, in order to generate effective ultrafiltration during CAPD, the glucose concentration (75 to 214 mmol/L) must typically be 15 to 40 times physiological levels (within the range of 1500 to 4250 mg/dL). There is growing concern that the continuing and long-term chronic exposure to high levels of glucose has serious adverse metabolic effects on peritoneal tissues. It has been noted that tissues from long-term PD patients bear pathologic alterations strikingly similar to diabetiform vascular disease, with a thickening of the basement membrane, vascular alterations, and AGE deposition [38–41]. An overview of peritoneal glucotoxicity—mechanisms by which glucose directly or indirectly affects structural and functional alter-

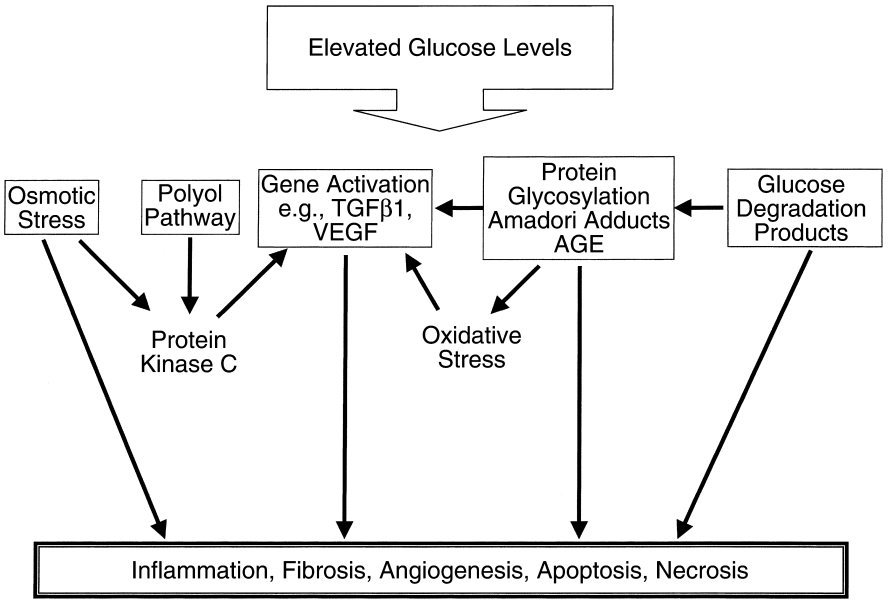

Fig. 2. Mechanisms of peritoneal glucotoxicity. Abbreviations are: TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; AGE, advanced glycation end products. (Reprinted from reference [33] with permission of *Peritoneal Dialysis International*.)

ations in the membrane—is shown in Figure 2 and is summarized below.

High glucose-mediated changes in mesothelial cell gene expression noted in cell culture assays may be causally related to changes in peritoneal membrane structure and function. High glucose is able to up-regulate transforming growth factor-β (TGF-β) [42, 43] and fibronectin [44, 45] mRNA and protein expression in mesothelial cells. In addition, the subsequent activation of vascular endothelial growth factor (VEGF) by TGF-β in human [abstract; Witowski et al, *Perit Dial Int* 21(Suppl 1):S21, 2001] and rat [46] peritoneal mesothelial cells suggests a relationship between high glucose exposure, peritoneal fibrosis, and changes in transport seen in long-term patients and in a rat model of TGF-β overexpression [46]. High glucose, TGF-β, and hyperosmolarity all may contribute to damaged intercellular junctions in human peritoneal mesothelial cells (HPMCs), suggesting that high glucose dialysate could induce peritoneal hyperpermeability and a progressive reduction in dialysis efficacy [47]. It also has been noted that high glucose up-regulates monocyte chemotactic protein-1 (MCP-1) in HPMCs [16]. As MCP-1 is a chemoattractant for peritoneal macrophages, major participants in peritoneal fibrosis through the synthesis of various cytokines and growth factors, it may provide an alternative route to mediate peritoneal fibrosis. And finally, the effects of high glucose on the generation of reactive oxygen species (ROS) in HPMCs have been reviewed [48]. ROS serve as signaling molecules for protein kinases and transcription factors including nuclear factor-κB (NF-κB) and, as such, their up-regulation by high glucose may be important in altering patterns of gene activation (for example, TGF-β and fibronectin) in peritoneal tissues.

The glucose-mediated up-regulation of molecular pathways in mesothelial cells most likely has a significant role in peritoneal membrane dysfunction [26, 33, 48–51]. The direct effects on the polyol pathway and specific genes such as protein kinase C (PKC), TGF-β, VEGF, and MCP-1 are thought to facilitate the development of peritoneal fibrosis and extracellular matrix (ECM) expansion and increased angiogenesis, which are strongly suspected to result in altered ultrafiltration over time. Exposure of the membrane components to high glucose also can have an indirect effect on membrane function, through AGE formation leading to subsequent alterations in the mesothelial, interstitial, and endothelial layers of the membrane (detailed later in this article) [52–54].

One of the anticipated benefits of icodextrin is being able to reduce the level of peritoneal membrane glucose exposure. This has the potential to significantly minimize many of the glucose-related cytotoxicities, and therefore better preserve normal membrane physiology as it relates to the ability of the membrane to function effectively as a dialysis membrane.

HYPEROSMOLAR STRESS

Glucose-based PD solutions are significantly hyperosmolar relative to serum, while icodextrin at 282 mOsm is iso-osmolar to normal plasma (Table 2). There are numerous in vitro studies that detail how peripheral blood and peritoneal leukocytes and mesothelial cells are adversely affected by exposure to hyperosmolar solutions (Table 3). In an early study designed to evaluate the biocompatibility of iso-osmolar solutions, de Fijter et al demonstrated improved phagocytic and respiratory burst activity in both polymorphonuclear cells and monocytes

Table 3. Effects of glucose and icodextrin on different cell types

	Glucose	Icodextrin	References
Mesothelial cells	Increased PGE_2 expression[a]	No change in PGE_2 expression[a]	[18]
(primary culture)	tPA induction[a]	No change in tPA[a]	[55]
Mesothelial cells	Abnormal morphology[c]	Normal morphology[b]	[56]
(from effluent)	Reduced proliferation[c]	Improved proliferation[b]	[56]
Polymorphonuclear cells	Cytotoxicity[a]	No significant cytotoxicity[a]	[57]
(peripheral blood)	Reduced phagocytosis[a]	Increased phagocytosis[b]	[58]
	Reduced respiratory burst[a]	Increased respiratory burst[b]	[58, 59]
	Reduced superoxide production[a]	Increased superoxide production[b]	[59]
	Reduced leukotriene B_4 synthesis[a]	Increased LTB_4 synthesis[b]	[60]
Monocytes	Reduced phagocytosis[a]	Increased phagocytosis[b]	[58]
(peripheral blood)	Reduced respiratory burst[a]	Increased respiratory burst[b]	[58, 59]
	Reduced superoxide production[a]	Increased superoxide production[b]	[59]
Macrophages	Reduced phagocytosis[c]	Increased phagocytosis[b]	[58]
(from effluent)	Reduced respiratory burst[c]	Increased respiratory burst[b]	[58]

[a] Compared to control
[b] Compared to glucose solution
[c] Compared to icodextrin solution

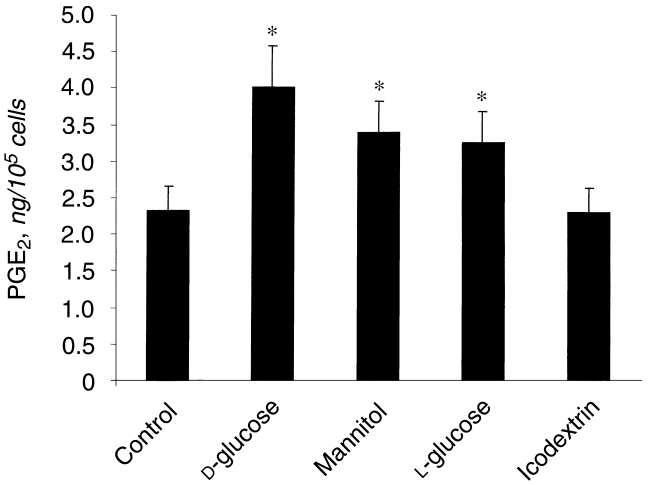

Fig. 3. Icodextrin does not affect prostaglandin E_2 (PGE_2) synthesis in cultured human peritoneal mesothelial cells (HPMCs). HPMCs were incubated for 24 hours in culture medium containing 2% human serum and D-glucose, mannitol, or L-glucose (each at 90 mmol/L) or icodextrin (7.5%). Control cells were incubated in medium plus serum. PGE_2 in culture medium was measured by ELISA. Values are mean ± SEM, $N = 7$. $^*P < 0.05$ compared to control. Figure is adapted from Sitter et al [18] with permission from the American Society of Nephrology.

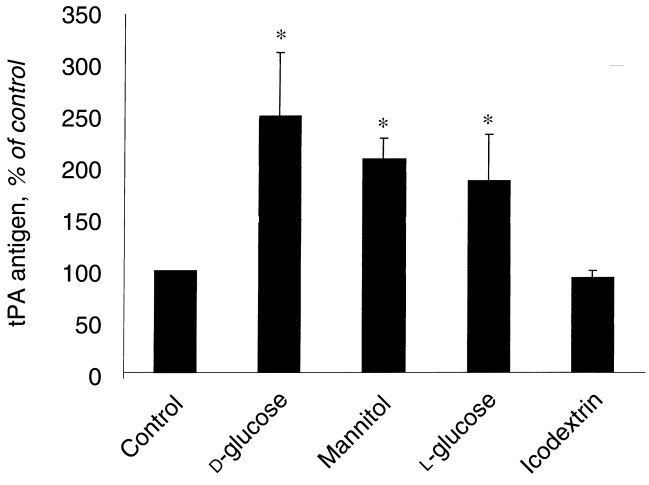

Fig. 4. Icodextrin does not affect tissue plasminogen antigen (tPA) synthesis in cultured human peritoneal mesothelial cells. HPMCs were incubated for 24 hours in culture medium containing 2% human serum and D-glucose, mannitol, or L-glucose (each at 90 mmol/L) or icodextrin (7.5%). Control cells were incubated in medium plus serum. Levels of tPA antigen in culture medium were measured by ELISA. Values are mean ± SEM, $N = 5$. $^*P < 0.05$ compared to control. Figure is adapted from Sitter et al [55] with permission from *Thrombosis and Haemostasis*.

exposed to icodextrin versus glucose-based solutions [58], implying improved biocompatibility of icodextrin. When the effect of hyperosmolarity was studied in mesothelial cells, Sitter et al showed that the synthesis of prostaglandin E_2 (PGE_2) in cultured mesothelial cells exposed to icodextrin (7.5% in culture medium) was unchanged relative to control, but was significantly increased in cells exposed to 90 mmol/L D-glucose (Fig. 3) [18]. Increased PGE_2 is associated with protein loss in the peritoneum [61] and with macrophage cytokine down-regulation [62]; normalization of PGE_2 levels through the use of iso-osmolar icodextrin therefore may contribute to improved membrane function and host defense. It has also been demonstrated that tissue-type plasminogen activator (tPA) induction in HPMCs was dependent mainly on hyperosmolarity and mediated through PKC while, in contrast, icodextrin did not affect tPA production, and therefore may not play as direct a role in mediating the fibrinolytic balance in the peritoneal cavity (Fig. 4) [55]. Hyperosmolar glucose exposure was shown to enhance the expression of aquaporin-1 (AQP-1) mRNA and protein in cultured human peritoneal mesothelial cells [26] and increase the abundance of AQP-1 protein in the plasma membrane of cultured rat peritoneal mesothelial cells [51]. Aquaporins are expressed by a number of cell types including peritoneal endothelial and meso-

thelial cells, and are thought to be equivalent to the ultrasmall water pores of the peritoneum specific for water transport. While they may play an important role in dialysis adequacy and fluid balance in peritoneal dialysis, their role, if any, in ultrafiltration failure is still unknown [63]. Finally, Ha et al reported that icodextrin and glucose-based solutions had similar effects in mesothelial cells on cell proliferation, DNA damage and cytotoxicity [48]. These authors found that HPMC proliferation appeared to be more affected by high osmolarity than were cytotoxicity or DNA damage, which were more sensitive to low pH and/or high GDP levels.

There have been numerous studies evaluating the impact of PD solutions on cellular functions that do not specifically identify hyperosmolarity as the causative factor. Thomas et al observed enhanced respiratory burst activity as well as increased superoxide anion generation in polymorphonuclear cells and monocytes with icodextrin-containing solutions [59]. In their study, the bactericidal activity of polymorphonuclear cells was improved in icodextrin compared to 1.5% glucose, with no difference in monocytes. There was no difference in phagocytosis in either cell type. While the authors attributed the differences observed to low osmotic stress with icodextrin, they were not able to rule out the possible contributions of glucose toxicity or GDP toxicity in the glucose solutions tested. Overall, these studies suggest an improved biocompatibility profile for icodextrin. In a study conducted by Jörres et al, there was no difference in cytokine release and mRNA synthesis in polymorphonuclear cells exposed to icodextrin and glucose-based PD solutions [57]. However, these authors found no significant cytotoxicity of icodextrin-based solutions, while both low and high glucose PD solutions were significantly cytotoxic compared to the control medium. Liberek et al reported mixed results with higher toxicity in polymorphonuclear cells, no change in phagocytosis and respiratory burst, and improved leukotriene B_4 synthesis in icodextrin versus high glucose PD solution [60]. Plum et al observed reduced cytokine release in monocytes exposed to the icodextrin solution prepared in their laboratory [64], but their results must be interpreted with caution as the polymer studied was purchased from a chemical supply company and therefore was not representative of the glucose polymer used in icodextrin-based PD solution.

While cell culture studies are useful in elucidating mechanisms of PD solution-mediated cytotoxicity, they are equivocal at best in establishing superiority of icodextrin versus glucose. Ex vivo and in vivo studies are more likely to predict the clinical relevance of biocompatibility. In an ex vivo study, peritoneal macrophages isolated from PD patients' icodextrin effluents exhibited significantly enhanced phagocytic capacity and chemiluminescence response compared to cells from glucose effluents [58]. Mesothelial cells collected from an overnight exchange in icodextrin had a more normal morphology and greater proliferation capacity than cells from the same patients collected from an overnight 2.27% glucose (2.5% dextrose) exchange (Fig. 5) [56], suggesting improved biocompatibility with icodextrin. In contrast, in a mouse model Gotloib et al observed decreased peritoneal mesothelial cell density and viability after intraperitoneal exposure to both glucose- and icodextrin-based solutions [65]. The authors attributed these cytotoxic effects to glucose, GDP, and AGE-mediated oxidative stress, but as those factors are absent or very low in icodextrin-based solutions, the basis of their conclusions may be unfounded.

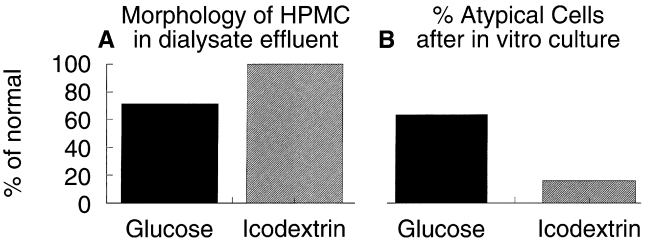

Fig. 5. Icodextrin preserves mesothelial cell viability and morphology. HPMCs recovered from dialysis effluents after an overnight dwell using either icodextrin- or glucose-based solutions were evaluated for cell viability and morphology. HPMCs from icodextrin effluent show a greater percentage of total cells with a normal morphology than those recovered from glucose effluent (*A*) and fewer cells with atypical morphology after culture in vitro (*B*). Data are derived from Bajo et al (abstract; *Nephrol Dial Transplant* 14:A249, 1999).

Finally, in a prospective clinical study designed to examine the outcome of long-term exposure to icodextrin, Posthuma et al evaluated peritoneal membrane transport kinetics, membrane markers [66] and parameters of host defense [67] in continuous cyclic peritoneal dialysis (CCPD) patients using either icodextrin or a glucose-based solution for the daytime exchange. The investigators found no difference in their patient populations over the course of two years for several indicators of host defense (phagocytic cell number, percentage, oxidative response, and cytokine production), but did see an improvement in phagocytosis of *S. epidermidis* and *E. coli* with icodextrin [67]. Peritoneal markers CA125, interleukin-8, and procollagen propeptides were stable over time, and membrane transport of low molecular weight solutes did not change over the course of the study [66].

GLUCOSE DEGRADATION PRODUCTS

One aspect of glucose-based solution bioincompatibility is attributed to the presence of GDPs. These low molecular weight compounds are generated primarily from the breakdown of glucose during the terminal heat sterilization process, and include acetaldehyde, formaldehyde, 2-furaldehyde, 3-deoxyglucosone (3-DG), glyoxal, methyglyoxal, 5-hydroxymethyl-furfural and probably

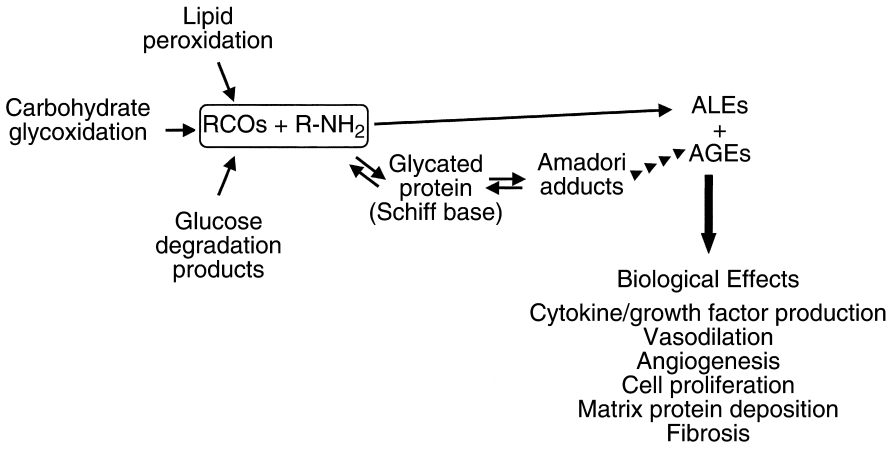

Fig. 6. Formation and biological effects of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs). Reactive carbonyl compounds (RCOs) are derived in uremia from the glyoxidation of carbohydrates, and are present among the glucose degradation products found in standard PD solutions. RCOs react with proteins to form Schiff bases via glycation and Amadori adducts via rearrangements. These early nonenzymatic events occur within days and are reversible. Over a period of weeks, the irreversible process of advanced glycation occurs via further rearrangements and cross-linking, resulting in the formation of AGEs. AGEs, and to a lesser extent the Schiff base and Amadori adducts, may contribute to the biological effects of glycation. RCOs derived from lipid peroxidation react with proteins to form advanced lipoxidation endproducts (ALEs), which share the biological activities of AGEs. R = protein.

Table 4. Range of concentrations of glucose degradation products measured in glucose- or icodextrin-based PD solutions

		Concentration *μmol/L*		
Compound	Formula	Glucose-based solutions	Icodextrin-based solution	References
Acetaldehyde	C_2H_4O	120–420	35	[79, 80]
3-DG	$C_6H_{10}O_5$	47–118	4.1	[75, 78]
Formaldehyde	CH_2O	4.6–15	ND	[70, 72]
2-Furaldehyde	$C_5H_4O_2$	0.05–2	ND	[80]
Glyoxal	$C_2H_2O_2$	3.0–14	2.6	[80]
5-HMF	$C_6H_6O_3$	2.2–30	ND	[70, 72]
Methylglyoxal	$C_3H_4O_3$	2.0–22.7	1.9	[70, 78, 80]

Glucose-based solutions were commercially available, heat-sterilized solutions containing 1.36% glucose (1.5% dextrose). Icodextrin-based solution was commercially manufactured, heat-sterilized solution containing 7.5% icodextrin. ND is not determined.

Table 5. Direct comparison of glucose degradation product concentrations in icodextrin- and glucose-based dialysis solutions

Compound *μmol/L*	Glucose (1.36 %)	Icodextrin	*P* value
Glyoxal	6.2 ± 0.5	2.6 ± 1.2	<0.01
Methylglyoxal	7.8 ± 0.6	1.9 ± 0.5	<0.001
3-DG	47.2 ± 4.3	4.1 ± 0.7	<0.001
Total RCOs	64.7 ± 8.7	26.4 ± 4.5	<0.01

Data are taken from [71]. Data are duplicate determinations from three independent batches expressed as mean ± SD. Statistics by the Student *t* test or ANOVA; $P < 0.05$ is considered statistically significant. RCOs are reactive carbonyl compounds.

additional as yet unidentified compounds [68–71]. GDPs are thought to exert their effects via two mechanisms: either by direct cytotoxicity (for example, inhibition of cell proliferation), as noted in vitro with formaldehyde, acetaldehyde, and methylglyoxal [72, 73], or indirectly by accelerating the process of AGE formation as seen with reactive carbonyl compounds (RCOs) such as glyoxal, methylglyoxal, and 3-DG (Fig. 6 and next section) [74–77]. Icodextrin-based solutions, by virtue of the replacement of glucose with glucose polymer, have extremely low levels of individual GDPs and total RCOs (Tables 4 and 5) [54, 78, 79].

Witowski et al used primary cultures of human mesothelial cells to confirm the cytotoxic potential of GDPs [73, 81], previously explored in transformed fibroblast cell lines and in peripheral and peritoneal leukocytes [68, 82]. They concluded that GDPs (acetaldehyde, formaldehyde, 2-furaldehyde, glyoxal, 5-hydroxymethyl-furfural, or methylglyoxal) pose a significant cytotoxic potential toward HPMCs. While individual GDPs did not impair viability, combinations of GDPs as found in PD solutions were cytotoxic, and their effects would most likely be cumulative over time versus acute or short-term exposure [73, 81]. In a study on cell viability, icodextrin supported improved proliferation of murine fibroblasts compared to a high-glucose standard PD solution (both solutions were heat-sterilized and adjusted to neutral pH) [79], the difference being attributed to the lower levels of GDPs in icodextrin versus the glucose-based solution.

PERITONEAL AGE FORMATION AND CARBONYL STRESS

It has been proposed that the peritoneal cavity of PD patients is in a state of severe overload of carbonyl stress compounds derived not only from glucose-based dialysis solutions (GDPs), but also from the uremic circulation [83]. Reactive carbonyl compounds, or RCOs, are generated in uremic plasma from both carbohydrates and lipids by oxidative and non-oxidative processes. Glucose and reactive carbonyl compounds (GDPs) from dialysis solutions, together with uremic derived RCOs, can react

with proteins to form AGEs and advanced lipoxidation end products (ALEs; Fig. 6).

Advanced glycation end products and ALEs have been implicated in a variety of activities that may compromise normal membrane function, including protein and extracellular matrix cross-linking, inflammation, chemotaxis [84], angiogenesis [85], vascular smooth muscle cell proliferation [86], and increased nitric oxide (NO) production [87]. In experiments related to diabetic retinopathy, pathophysiologically relevant levels of AGEs induced VEGF mRNA and protein expression in retinal pigment epithelial cells and in bovine vascular smooth muscle cells in a dose and time dependent fashion [85], suggesting a link between hyperglycemia, AGE formation, and VEGF. These events may serve as a model for glucose-mediated modifications that affect both peritoneal membrane structure (such as fibrosis) and function (such as increased effective peritoneal surface area), which in turn can lead to increased permeability for glucose and small solutes, and eventually result in ultrafiltration failure [88]. AGEs and ALEs have been localized to the peritoneal membrane of normoglycemic uremic patients prior to the initiation of PD, a finding that supports the contribution of both uremia and increased oxidative stress to AGE formation and membrane alterations [54], and suggests that this process is at least partially independent of glucose.

A direct correlation between duration of PD and peritoneal tissue AGE content has been described, suggesting that the increased AGE/ALE staining in long-term patients was potentially due to the glucose-mediated mass transfer of RCOs across the peritoneal membrane with subsequent deposition in peritoneal tissues, and that AGE-induced vascular changes in the membrane were directly related to increased membrane permeability [89]. Honda et al noted that AGE deposition correlated with increasing severity of interstitial fibrosis and vascular sclerosis, raising the possibility that AGE accumulation enhanced the progression of peritoneal fibrosis and vascular changes, resulting in impaired ultrafiltration capacity [52]. All of these studies suggest a strong causal relationship between the uremic state, duration of dialysis, AGE-mediated membrane alterations and the decline of ultrafiltration. It is in this context that we now review the potential role that icodextrin may play in GDP- and AGE-associated membrane changes.

GLYCATION OF PERITONEAL PROTEINS, AMADORI ADDUCT AND AGE FORMATION

Glucose is associated with the non-enzymatic glycation of proteins in vitro [90], a process that indirectly leads to the formation of Amadori adducts. AGEs have been shown to reduce the HPMC viability in vitro in a dose-dependent fashion [53]. The binding of glycated albumin

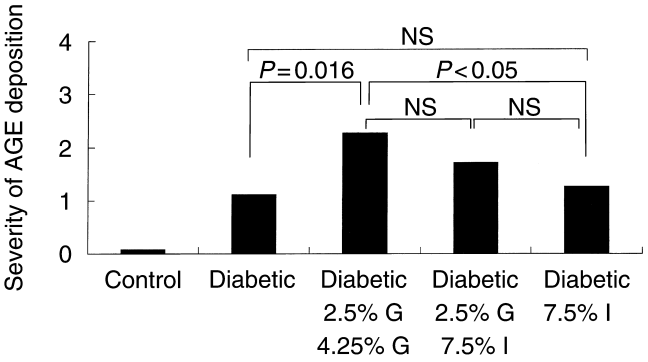

Fig. 7. AGE deposition is reduced in icodextrin- versus glucose-treated diabetic rats. AGE accumulation in the peritoneal membrane of normal and streptozotocin-induced diabetic rats was measured after 12 weeks exposure to various dialysis solutions [2.27% glucose (2.5% dextrose) and 3.86% glucose (4.25% dextrose) or 7.5% icodextrin]. AGE deposition was most severe in the group exposed only to glucose-based fluid ($P = 0.016$ vs. control diabetics), while deposition in the icodextrin group was significantly less than the glucose group ($P < 0.05$), and not significantly different from the control diabetics. Data reprinted from Lee et al [96] with permission from the Society of Peritoneal Dialysis.

to the AGE receptor (RAGE) in human peritoneal mesangial cells (HPMCs) resulted in enhanced vascular cellular adhesion molecule (VCAM-1) expression and leukocyte adhesion [91]. This suggests a mechanism by which AGEs contribute to inflammatory processes in the peritoneal cavity. There is evidence from several studies for a decreased rate of formation of glycated and AGE-modified protein in vitro with icodextrin- versus glucose-based PD solutions [92–95]. Amore et al have found apoptotic indices and inducible nitric oxide synthase (iNOS) activity in HPMCs exposed to icodextrin equivalent to control basal levels as opposed to cells exposed to glucose-based solutions, attributing the improved biocompatibility to reduced Amadori adduct formation (abstract; *J Am Soc Nephrol* 9:278A, 1998).

The lower potential of icodextrin for in vitro glycation of proteins and for AGE formation is beginning to be borne out in animal studies. A significantly reduced level of peritoneal membrane AGE staining was reported in normal rats dialyzed with icodextrin versus 2.27% glucose (2.5% dextrose) solution, as well as a reduction in both membrane thickness and TGF-β staining, indicating a less fibrotic and by definition, a more biocompatible physiology (abstract; Kim et al, *J Am Soc Nephrol* 10: 317A, 1999). Lee et al has recently reported that diabetic rats dialyzed with icodextrin had significantly lower peritoneal AGE staining than did rats dialyzed with glucose (Fig. 7) [96], underscoring the potential of icodextrin for minimizing AGE-mediated membrane alterations.

In a prospective clinical study, Posthuma et al found that while icodextrin reduced the formation of Amadori albumin and AGE protein in vitro, there was no difference in effluent levels of early (Amadori albumin) or ad-

vanced (AGE-derived fluorescence) markers in CCPD patients using icodextrin or glucose-based solutions for their daytime dwells over a two year period [95]. In a short-term study conducted by Ho-dac-Pannekeet et al, the levels of the advanced glycation marker pentosidine in effluents of patients using glucose- or icodextrin-based PD solutions essentially confirmed Posthuma et al's findings of no significant differences in the two patient populations [97]. The authors of both studies attributed the lack of difference in glycation and/or AGE levels in the icodextrin and glucose effluents to "washout" of compounds from the peritoneal tissues during the dwell, a phenomenon observed previously [54, 78].

These studies suggest that during PD there is bi-directional movement of both RCOs and AGE-modified proteins across the peritoneal membrane. There appears to be an influx of GDPs and RCOs from the solution into the tissue, and an outflow of total RCOs and AGEs from the tissues and circulation into the effluent, that is, the "washout" referred to by these authors. The variables being measured in these studies—effluent glycation and AGE protein levels—are more indicative of ongoing *trans*-membrane transport than the state of permanent membrane modification. Thus, interpretation of these results is limited, as they would not accurately reflect membrane AGE content or, more importantly, membrane structural changes associated with AGE formation.

In addition, all of the patients in these studies used glucose-based solutions prior to beginning the study, and by necessity continued to use them for their non-icodextrin exchanges. Therefore, their persistent exposure to glucose and elevated GDPs may have overwhelmed the biocompatibility impact of the icodextrin exchange. Second, the time on study was too short to see an effect, certainly in the Ho-dac-Pannekeet study, but probably also in the Posthuma study; the authors acknowledge this in a subsequent publication on the same study [66]. AGE accumulation in the membrane occurs over time and the subsequent AGE-mediated changes in membrane structure and function take even longer for their effects to become measurable. It is known that substantial changes in small solute transport and reductions in ultrafiltration appear only after three to four years on conventional solutions [98], and we would expect that to hold true here.

Ho-dac-Pannekeet et al also reported that in five out of six patients with ultrafiltration failure, a six-week regimen of non-glucose dialysis (the specifics of the solutions were not detailed) resulted in decreased effluent pentosidine levels; the differences approached but did not achieve statistical significance [97]. The results of their study strongly implicate ongoing glucose exposure in the glycation of peritoneal proteins, and suggest that if glucose and/or GDP exposure is more effectively eliminated, there might be an avenue for reducing in vivo glycation and AGE formation.

BIOCOMPATIBILITY OF ICODEXTRIN

We have now reviewed the effects of icodextrin and glucose-based solutions on cell and membrane functions in numerous in vitro, ex vivo, and in vivo studies. The biocompatibility of icodextrin can be addressed in two ways: first, in a very straightforward fashion by determining how the initial biocompatibility criteria have been met and what the assessment seems to be; and secondly, and just as importantly in the long run, by determining how icodextrin fits into a much broader therapeutic strategy of enhancing PD.

The formulation of icodextrin-based PD solution does address three of the four biocompatibility factors in a manner to suggest improved biocompatibility. Of the four factors, only low pH/lactate is not corrected in its formulation. Since icodextrin is a long dwell solution, with one exchange over a 9 to 12 hour period with seemingly rapid equilibration of pH upon instillation, the effect of low pH would be minimized over the time of the exchange. Due to its formulation as an iso-osmotic solution, the biocompatibility disadvantages with hyperosmolarity are avoided. Replacing glucose with icodextrin eliminates the issues of direct glucotoxicity and clearly reduces the GDP content.

We have calculated the potential reductions in both peritoneal membrane glucose exposure and GDP absorption we would achieve through the use of icodextrin for the long dwell exchange (Fig. 8). These calculations assume a CAPD regimen of three 2.5-L exchanges with 1.36% glucose (1.5% dextrose) and an overnight exchange of either 7.5% icodextrin or 3.86% glucose (4.25% dextrose). With a reduction in daily peritoneal membrane glucose exposure of 48.6%, and decreases of 48%, 47%, and 24% in peritoneal absorption of 3-DG, glyoxal, and methylglyoxal, respectively (the three GDPs that appear to be most reactive in contributing to AGE formation), the use of icodextrin should be strongly recommended for reducing the potential avenues of glucose-induced toxicity, and GDP-mediated AGE formation and peritoneal membrane alterations.

Icodextrin appears to be more biocompatible than glucose-based solutions in that it has fewer detrimental effects on normal cell and membrane function as demonstrated in a variety of in vitro, ex vivo, and in vivo assays. Several incongruous case reports of sterile peritonitis associated with the use of icodextrin-based PD solution have been reported to date [99–102], the cause of which is currently under study. Nonetheless, with over 9000 patients using icodextrin-based solution worldwide at the time of this review, it appears to be a safe and well-tolerated PD therapy.

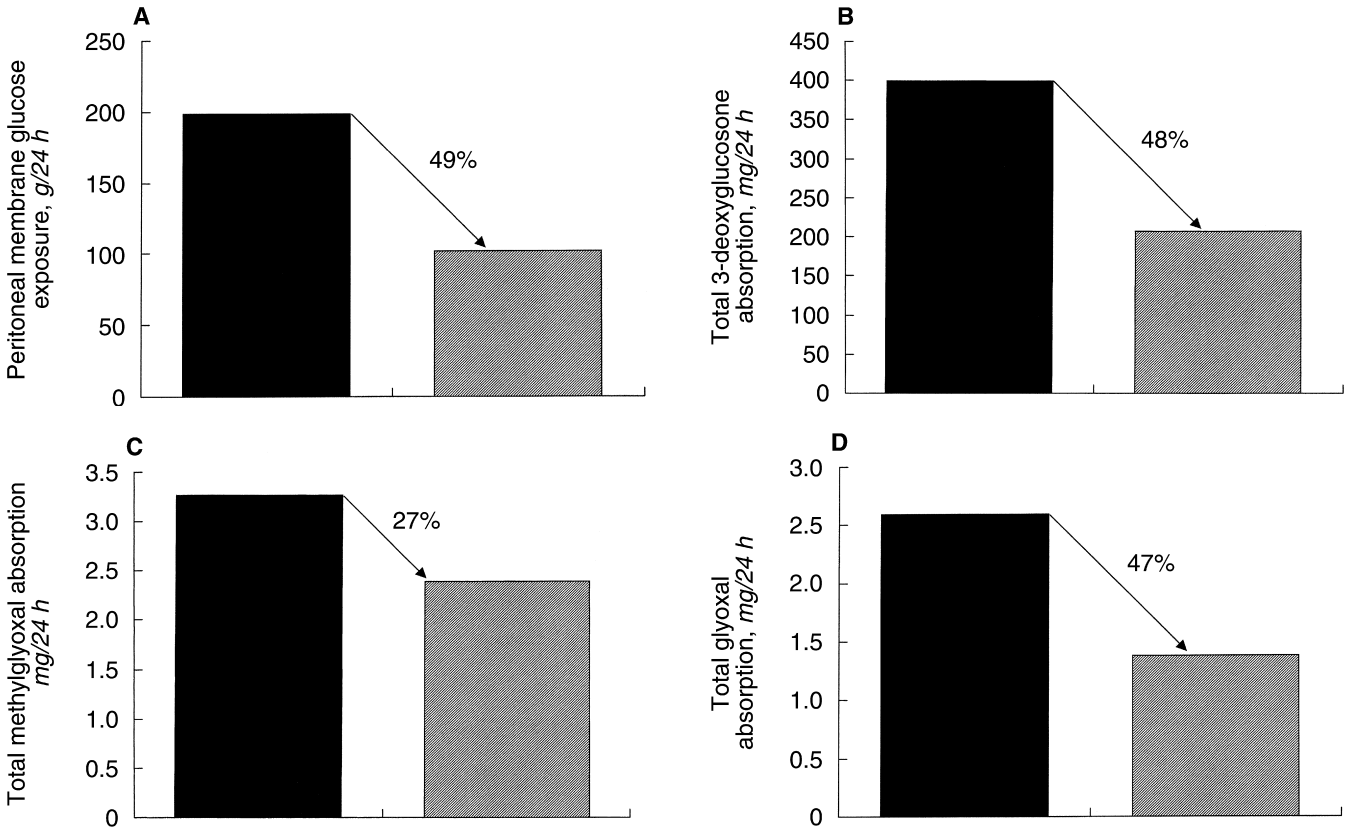

Fig. 8. Potential reduction in peritoneal membrane glucose and GDP exposure with icodextrin. Peritoneal membrane exposure to glucose and GDP absorption was based on an assumed daily regimen of three 5-hour dwells of 1.36% glucose (1.5% dextrose) and a 9-hour dwell of either 7.5% icodextrin (■) or 3.86% glucose (■; 4.25% dextrose). Peritoneal glucose exposure was calculated assuming total glucose absorption for each dwell. GDP absorption was calculated for 3-DG, methylglyoxal, and glyoxal from the addition of the AUC values for each exchange over 24 hours and the kinetics of clearance of GDPs from Miyata et al [54]. Differences between glucose and glucose/icodextrin regimens are given as a percent decrease.

The strategy for improving the biocompatibility of PD solutions relies on an understanding of the relationship between the patient, the solution, and the membrane. It is a complex inter-dependency with all three components influencing the biocompatibility of the dialysis therapy. Much of the focus on icodextrin's biocompatibility has been on the removal of glucose and subsequent reduction of all of the glucose-mediated events. We must not forget that the uremic milieu and PD solutions are co-contributors to membrane dysfunction through both glucose-related toxicities and carbonyl/oxidative stress. It must be recognized and understood how each of these entities contributes to compromised membrane performance before the appropriate therapeutic strategy may be adopted.

STRATEGY TO IMPROVE PERITONEAL DIALYSIS

The overall strategy to improve PD therapy, therefore, should encompass a multi-component approach, with biocompatibility of a solution just one part of a larger strategy. A complete regimen would include the use of biocompatible solutions for all exchanges: the use of icodextrin as the long dwell exchange, with its associated reduction in glucose and GDP exposure, along with the use of low glucose or low GDP solutions in all other exchanges. Patients might undergo more rigorous monitoring for glycemic control to minimize systemic glucotoxic effects. There are AGE blockers, AGE cross-link breakers, and RCO scavengers in pre-clinical or clinical development that could be extremely valuable in preventing or reversing not only solution, but uremic RCO-mediated membrane alterations [88]. In addition, a well-defined system of monitoring outcomes, either through clinical trials or a biopsy registry [103], is essential. Ultimately, the value of improved biocompatibility through the use of novel solutions such as icodextrin will be demonstrated by the success of the overall therapy in which the solution plays an integral role.

ACKNOWLEDGMENT

The authors thank Dr. Steph Morti for calculating the differences in peritoneal membrane glucose and GDP exposure.

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APPENDIX

Abbreviations used in this article are: AGE, advanced glycation end product; ALE, advanced lipoxidation end product; APD, ambulatory peritoneal dialysis; AQP-1, aquaporin-1; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cyclic peritoneal dialysis; 3-DG, 3-deoxyglucosone; GDP, glucose degradation product; HPMCs, human peritoneal mesothelial cells; iNOS, inducible nitric oxide synthesis; MCP-1, monocyte chemoattractant protein-1; PD, peritoneal dialysis; PGE_2, prostaglandin E_2; PKC, protein kinase C; RAGE, receptor to advanced glycation end product; RCO, reactive carbonyl compounds; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; tPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

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